A STUDY OF POST TRANSPLANT PULMONARY INFECTIONS

Dissertation submitted in partial fulfilment

of the requirements for the degree of

D.M. (Nephrology)

Branch III

THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY
CHENNAI

AUGUST 2007

ACKNOWLEDGEMENT

I would like to express my sincere gratitude to my beloved Professor ***M. Jayakumar MD.DM***, Professor and Head, Department of Nephrology, Madras Medical College for his motivation, advice, guidance and valuable criticism which enabled me to complete this work.

My sincere thanks to my Assistant Professors ***Dr. M. Edwin Fernando, MD, DM, Dr. Venkatraman***, ***M.D, DM, Dr. R. Manorajan MD, DM, Dr. V.Balaraman, MD, DM, Dip NB*** and ***Dr. T. Balasubramaniyan***, ***MD, DM,*** for their co- operation and guidance

I thank ***Mr. Venkatesan,*** for his help in statistical analysis.

CERTIFICATE

This is to certify that this dissertation entitled ' A Study of Post Transplant Pulmonary Infections' submitted by Dr. N. Malathy, appearing for D.M. Nephrology degree examination in August 2007 is a bonafide record of work done by her under my direct audience and supervision in partial fulfilment of regulation of the Tamil Nadu Dr. M.G.R. Medical university, Chennai, I forward this to the Tamilnadu Dr. M.G.R. Medical university, Chennai, Tamilnadu, India.

Prof. M. JAYAKUMAR M.D., D.M.
Professor and Head
Department of Nephrology
Madras Medical college &
Govt. General Hospital
Chennai - 600003

DEAN,
Madras Medical College,
Chennai - 600 003.

CONTENTS

AIM OF THE STUDY

1. To determine the incidence and period in which post transplant pulmonary infections occur in our centre
2. To analyse the microbiological pattern of post transplant pulmonary infections and its outcome
3. To determine the risk factors for developing post transplant pulmonary infections
4. To determine the clinical profile of pulmonary infections in post transplant patients
5. To determine the usefulness and the pattern of lesions by Imaging techniques (X-ray chest and CT Chest)
6. To assess the utility of Broncheoalveolar lavage in the management of Post transplant pulmonary infections.

MATERIALS & METHODS

A RETROSPECTIVE STUDY

Case records of patients transplanted between January 2000 and December 2006 who had pulmonary infection were included in this study.

Pulmonary infection is defined as

1. Fever > 100^0 with cough > 3 days duration

   or

2. Abnormality of chest X ray

   or

3. Abnormality of CT Chest.

The pulmonary infections were classified and analysed under the following headings based on the etiologic infective agent.

1. Bacterial (non-tuberculous) infections.
2. Mycobacterial infections.
3. Atypical mycobacterial infections.
4. Fungal infections.

The period of occurrence of pulmonary infection was analysed in the following manner.

1. <1month
2. 1 to 6 months
3. 7 to 12 months
4. > 12 months

The following risk factors were studied:

1. Anti rejection therapy (ART)
2. Post transplant diabetes mellitus (PTDM)
3. Cytomegalovirus (CMV) infection
4. Hepatitis C (HCV) infection
5. Leucopenia

The relationship of these risk factors towards the development of pulmonary infections were also analysed.

The radiological abnormalities in the X-ray chest and CT scan were stratified as unifocal and multifocal lesions[21] and were analysed separately.

The following investigations were done with sputum and BAL fluid

1. Gram stain
2. AFB stain
3. KOH mount
4. Bacterial culture
5. Mycobacterial culture
6. Fungal culture

The outcome was measured in terms of graft dysfunction and mortality

Variables were analyzed with Chi-square test , Fischer's confidence interval and Two Sample Binomial Proportion Test.

REVIEW OF LITERATURE

INTRODUCTION

Infectious complications are major causes of morbidity and mortality following organ transplantation. The success of renal transplantation depends on a compromise between achieving sufficient immunosuppression to avoid rejection of the graft and maintaining a sufficient level of immune competence to protect the recipient from infection. In the early years of transplantation, the incidence of severe and lethal infections was high and discouraging, but with increasing experience, a compromise gradually has been reached so that renal transplantation now offers equivalent or better patient survival to hemodialysis However, the problem of infection remains substantially of considerable concern[1].

The risk of infection in transplant recipients[2] is determined primarily by two factors:-

1. The intensity of exposure to potential pathogens (epidemiologic exposure)

2. The combined effect of all of the factors that contribute to patient susceptibility to infection (the net state of immunosuppression) [22,23].

Even minimal environmental exposure to organisms of low native virulence can cause invasive infection in a patient with maximal level of immunosuppression.

EPIDEMIOLOGICAL EXPOSURE

Epidemiologic exposure occurs in the community and in the hospital[22]. In the community, patients may have recent or remote contact with potential pathogens. Community exposure includes respiratory viruses, food borne pathogens and also includes recent and remote exposure to such organism causing geographically restricted mycoses, Mycobacterium tuberculosis, and Strongyloides stercoralis etc[22, 24]. Immunosuppression amplifies the effects of these infections, increasing the risk of tissue invasion, dissemination and superinfection[22,23].

In the case of systemic mycoses and tuberculosis, three patterns of disease are observed viz. Progressive primary infection; reactivation infection, and re- infection[25].Systemic dissemination is common with all three. These infections may present with fever of unknown origin, progressive pneumonitis or metastatic infections to other sites.

THE NET STATE OF IMMUNOSUPPRESSION

The net state of immunosuppression is the result of complex interaction among multiple factors;

1. Immunosuppressive therapy:-

   Dose, duration, and temporal sequence.

2. Underlying immune deficiency:-

   Autoimmune deficits, nutritional immune deficits

3. Integrity of the mucocutaneous barrier, catheters, epithelial surfaces

4. Devitalised tissue, fluid collections

5. Neutropenia, lymphopenia

6. Metabolic conditions:-

   - Uremia
   - Malnutrition
   - Diabetes
   - Alcoholism with cirrhosis

7. Infection with immunomodulating viruses:-

- Cytomegalovirus
- Epstein-barr virus
- Hepatitis B and C viruses
- Human immunodeficiency virus.

The sum of these factors constitutes the patient's net state of immunosuppression.

Although most infections in renal transplant recipients are caused by common pathogens, devastating opportunistic infections occur frequently enough to require a multidisciplinary approach involving infectious disease physicians and microbiologists.

INCIDENCE

The precise incidence of post-transplant infection is unknown because the definition may vary from the clinically significant and microbiologically, serologically or histologically proven episode to a positive culture report without clinical manifestations. Death from infection is an unreliable indicator of the size of the problem not only because infection can be a terminal event in a patient dying of

another cause, but also because most infections are treated successfully. Comparisons between units are hard to interpret without knowing the availability of maintenance hemodialysis facilities, which allow the irreversibly rejecting kidney to be abandoned early, or the selection criteria for transplantation of higher risk patients.

These caveats apart, the incidence of serious and lethal infection has fallen dramatically. In a study carried out in the early 1980s, Peterson and colleagues found that 32% of patients suffered a clinically significant infection; 7% of patients died, and in 87% of these deaths, infection was an important contributing factor[26]. By contrast, current studies report graft and patient survival of 85% and 95% at 1 year and 80% and 90% at 5 years, and cardiovascular events have overtaken infection as the leading cause of death[27]. Nevertheless, infection remains an important cause of mortality and allograft loss, particularly in patients who have suffered primary graft failure and undergo repeat transplantation. The reasons for the fall in the incidence of lethal and non-lethal infections include improvements in general clinical care arising from greater experience; improvements in methods of organ procurement, surgical technique and recipient selection and a greater awareness of the type

and timing of infections. Improved tissue matching may have contributed to lower rejection rates and to less intensive immunosuppression. A more conservative approach to immunosuppressive therapy is probably the most striking change in practice. Abandoning the effort to salvage the inexorably failing graft and in particular lower dose steroid therapy[28] have been shown to reduce the incidence of infection without causing poorer graft survival rates. Changing the immunosuppressive regimen needs to be monitored carefully to ensure that it does not increase unduly the risk of infection, but there is no evidence that any of the newer regimens has caused an increased incidence of infection.

Post transplant infections can be classified by the organism, the system involved or the time of appearance in relation to surgery[1].

TIME TABLE FOR INFECTION AFTER TRANSPLANTATION[2]

THIS IS ORGANISED INTO THREE SEGMENTS:-

1. The first month
2. One to six months
3. More than six months

Infection in the First month after Transplantation:

Three types of infection occur in the first month after transplantation. Rarely, active infection is conveyed with the allograft[2].Although unusual cases of disseminated toxoplasmosis or herpes simplex infection have resulted from the transplantation of organs from donors with active systemic infections. Untreated infection in the recipient can have a major impact after transplantation. In particular, transplantation of an organ into a patient with pneumonia or lung injury from pulmonary aspiration or infarction almost guarantees superinfection with nososcomial gram-negative bacilli, fungi or both[29].Cultures obtained from the donor and recipient at the time of transplantation are used to guide perioperative antimicrobial therapy. A basic tenet is that all infections should be eliminated before transplantation.

More than 90 percent of the infections occurring in the first month are the same nosocomial bacterial or candidal infections of the surgical wound, lungs, urinary tract, or vascular devices that occur in surgical patients who are not in a state of immunosuppression.

Notable by their absence in the first month after transplantation are such opportunistic pathogens as Pneumocystis carinii and Nocardia asteroides. The occurrence of infections with these pathogens during this month suggests the presence of an important nosocomial hazard, increased susceptibility resulting from immunosuppression before transplantation or pre-existing infection of the donor or recipient. Although the amounts of immunosuppressive drugs administered are greatest during this period, the main determinant of the net state of immunosuppression is the level of sustained immunosuppression rather than the short term effects of a particular immunosuppressive regimen[2]

INFECTIONS ONE TO SIX MONTHS AFTER TRANSPLANTATION

After the first month the nature of infectious diseases in transplant recipients changes. In addition to residual effects of earlier events, new types of infection appear. The immunomodulating viruses (particularly CMV, but also EBV, other human herpes viruses, HBV, HCV and HIV if present) begin to exert clinically significant effects. The combination of sustained immunosuppression and viral infection takes possible opportunistic infections due to Pneumocystis carinii, Aspergillus and Listeria monocytogenes in absence of an excessive epidemiologic hazard.

INFECTION MORE THAN SIX MONTHS AFTER TRANSPLANTATION

Six months after transplantation, patients can be divided into three categories in terms of their infectious-disease problems.

More than 80% of patients have a good result from transplantation and are maintained on minimal long-term immunosuppressive therapy with good allograft function. Their infectious –disease problems are similar to those of the general community and are primarily respiratory. Opportunistic infection is unusual unless a particularly intense environmental exposure has occurred (e.g., the occurrence of nocardiosis or aspergillosis after digging in the garden)

In 5 to 10 percent of transplant recipients, recurrent or chronic rejection develops, resulting in greater exposure to immunosuppressive agents, which often results in chronic infections. These patients are the most likely candidates for opportunistic infection, including infections with Pneumocystis carinii, Lister monocytogenes, Nocardia asteroides, Cryptococcus neoformans and Aspergillus. Lifelong prophylaxis with trimethoprim-sulfamethaxazole

careful attention to environmental exposure and consideration of antifungal prophylaxis are needed for these patients.

Overall, about 50% of infections are caused by viruses, 30% are caused by bacteria and 5% are caused by fungi. In 15% of cases, infection is polymicrobial.

PULMONARY INFECTION

Pulmonary infection is the most common form of tissue-invasive infection observed in transplant recipients. Important principle in treating these patients is that there is a reasonable chance of full rehabilitation if microbiologic cure is achieved .Early diagnosis and specific therapy is the cornerstone of cure. Therefore, invasive diagnostic techniques are justifiable in transplant recipients, the rule is to be aggressive in pursuing early diagnosis and specific therapy[22,23.]

Renal transplant patients suffer not only from respiratory infections that are common to normal persons and general hospital patients but also from opportunistic infection because of their defective cellular immunity. Pneumonia is a particularly important cause of illness and death in the renal transplant group. Because of the excellent outlook for transplantation itself, considerable effort at

expert diagnosis and management of complicating respiratory infection is mandatory[2].

The depressed inflammatory response of immuno-compromised transplant recipients may greatly modify or delay the appearance of pulmonary lesions on the radiograph. The presentation and evolution of the findings on chest radiography provides important clues to both the differential diagnosis of pulmonary infection in transplant recipients and the appropriate diagnostic workup

The known opportunistic organisms include fungi (such as P. carinii, aspergillus fumigatus and locally endemic types such as coccidioidomycosis and histoplasmosis), bacteria (Mycobacterium, Nocardia, Legionella and Pseudomonas), herpes viruses (especially CMV), protozoans (such as toxoplasmosis) and helminths (particularly Stongyloides). The following table is a practical rather than an exhaustive list of diagnosis possibilities.

PULMONARY INFILTRATES IN THE RENAL TRANSPLANT PATIENT[1]

Infection	*Others*
Bacteria Pneumococcus Staphylococcus Gram- negative bacteria Legionella Nocardia Mycobacteria Fungi Pneumocystis Aspergillus Candida Mucor Cryptococcus Virus Herpes viruses (especially Cytomegalovirus) Parasitic Strongyloides Toxoplasma	Pulmonary embolism Cardiovascular Pulmonary edema Pulmonary vasculitis Drug pneumonitis Tumor

Pneumocystis carinii has been a leading cause of potentially fatal pneumonia in many immuno-compromised groups. Before chemoprophylaxis programs, the annual attack rate of Pneumocystis in renal transplant recipients approached 20%. Opportunistic

Pneumocystis pneumonia is probably acquired as a fresh infection from an unidentified environmental source[14]. Pneumocystis produces a characteristically diffuse pneumonia with breathlessness, hypoxemia, fever and diffuse radiographic changes. Rapid diagnosis is essential because untreated it is uniformly fatal but shows an 80% response rate to prompt treatment. Because of its high attack rate in the renal transplant group, chemoprophylaxis against this infection has become an integral part of management schedules.

Aspergillus fumigatus is a hyphal saprophytic fungus in which infection is by inhalation of spores, and the lungs are the site of primary infection, although important complications such as hematogenous spread to the brain can ensue. Aspergillus can behave as a saprophyte in previously damaged lungs in persons with normal systemic immunity - as in allergic bronchopulmonary aspergillosis in asthmatics and mycetoma in old tuberculous cavities. In the immuno-compromised, aspergillus manifests as invasive aspergillosis producing pneumonia with the risk of hematogenous spread.

Nocardia asteroides is a gram-positive filamentous branching bacterium that normally is a soil saprophyte and is acquired by inhalation. Resulting disease is commoner in the immunosuppressed,

including renal transplant recipients[7]. The lung is the site of primary infection, where cavitating nodular shadows are most typical, but dissemination can occur to the brain and often is fatal.

Primary infection with Herpes simplex virus infections is rare. Reactivations, about 40% of which are asymptomatic (the virus being present in throat washings, or less commonly in the urine), are frequent. Case reports of fatal pneumonitis have been reported.

CMV infections are the most common viral infection affecting transplant recipients. About 2% progress to develop disseminated fatal disease. The usual cause of death in CMV infection is severe pneumonitis.

Influenza and respiratory syncytial virus infections cause even more disease than is usual in the renal transplant group-with resultant pneumonias with or without secondary infection by Pneumococcus or Staphylococcus.

Strongyloides stercoralis is a helminth with a unique autoinfection life cycle. Dormant infection, often acquired many years previously, can progress dramatically during immunosuppression to

produce a bronchus-obstructing and cavitating, hemorrhagic pneumonia, which can be accompanied by an enterocolitis[8].

Tuberculosis is encountered more frequently in renal transplant recipients than in the general population in all parts of the world[4] the prevalence of which is 5 – 50 times more than in the general population. Most cases of tuberculosis after renal transplantation are due to reactivation of old dormant tuberculosis[1]. Hence the incidence of post transplant tuberculosis can vary from region to region. The incidence of post transplant tuberculosis varies between 0.5 and 1% in the USA[4],1 and 4% in Europe and 3.5 % in Saudi Arabia. In contrast the incidence reported in India is between5% and 10%[4]. Mycobacterium tuberculosis is not properly an opportunist, but its control depends heavily on effective T-cell immunity. Renal transplant patients with no clinical or radiological suggestion of tuberculous disease at the time of transplantation, but in whom previous infection is likely because of the high endemicity of tuberculosis in their country of origin (e.g., the Indian subcontinent) suffer remarkably high rates of reactivation of old dormant tuberculosis during post-transplantation immunosuppression. Of this group, 25% can develop overt tuberculosis in the first 6 months after transplantation. Pulmonary disease is the commonest. Nodal, soft

tissue and hectic or subacute miliary illness may occur[9], and diagnosis requires expert histology or microbiology on direct tissue samples[10].

Atypical Mycobacteria has been increasingly recognized to cause pulmonary and nonpulmonary infections inpart by the increase in the number of susceptible hosts and inpart due to better recognition of their role through more sensitive and specific techniques.[31].These organisms can produce localized disease in the lungs, lymph glands, skin, wounds and bone. Occasionally they produce disseminated disease. Isolation of these bacteria from representive specimens and their rapid identification is very important as the treatment strategy for tuberculosis and other mycobacterioses is different.

CLINICAL PICTURE

Transplant recipients suffer simple episodes of acute bronchitis, common to everyone. The symptom of cough usually with purulent sputum may follow a simple viral rhinitis. There usually is little constitutional disturbance and few clinical and no radiographic signs in the chest, recovery may be spontaneous or follow a course of simple oral antibiotic.

More problematic is the patient with fever and radiographic pulmonary shadowing in whom there is threat to life and the differential diagnosis is broad and includes non- infectious disease. Some general points may help in suggesting a specific diagnosis. A timetable for different infections can be constructed based on the timing of the infection after transplantation Opportunistic infection is commonest during the peak of immunosuppression between 1 and 6 months post transplantation. Before and after this time, especially when there is good renal function accompanied by low-dose immunosuppression, infections typical of the general population, such as bacterial pneumonias, are commoner. Lymphoma presenting in the lung, can be a rare late complication. Geographical factors may be relevant, Infection with reactivation of endemic fungal disease, such as coccidioidomycosis or histoplasmosis, occurs in the Americas. Disseminated strongyloidiasis is seen in patients from many typical areas but especially in the West Indies and Far East[8]. Neutropenia means that infection with bacterial and fungal organism is at special risk.

Careful clinical review is of diagnostic value. High fever suggests infection, and clinical features of chills and shivers weigh against non-infectious diagnoses, such as cardiovascular pulmonary

edema, pulmonary embolism and alveolar haemorrhage. Pleurisy with pleural pain and pleural rub is not a feature of Pneumocystis pneumonia; cardiovascular pulmonary edema and alveolar haemorrhage are not features of this pneumonia. Pulmonary edema of cardiovascular origin may be suggested by marked orthopnea, the presence of gallop rhythm, elevated jugular venous pulse, peripheral edema, evidence of fluid retention from daily weighing and chart records and a chest radiograph showing a large heart and dilated pulmonary veins or septa. Such features usually establish a diagnosis of pulmonary edema, but difficulties often can be resolved by computed tomography (CT) scan or wedge pressure measurements.

Haemoptysis not only may be part of an infective syndrome but also must raise the possibility of pulmonary embolism and pulmonary haemorrhage, the latter particularly on a background of glomerulonephritis or of falling haemoglobin level. In pneumocystis pneumonia, fever and breathelessness often precede decisive radiographic changes, which eventually is typically diffuse and bilateral absence of physical signs in the chest is usual. Cytomegalovirus also causes a diffuse pneumonitis, which is a source of diagnostic confusion with pneumocystis. Patients who are ill with impaired consciousness, may suffer aspirational pulmonary

syndromes - an acid pneumonitis or anerobic infection. In general, the pace of the illness and character of the radiological change may provide important clues

APPROACH TO INVESTIGATION AND MANAGEMENT

Thorough clinical assessment, including a chest radiograph, is needed for all episodes of apparent respiratory infection in the renal transplant group. The scale of further investigation and management depends on the findings from this initial review.

a. Episodes of bronchitis with purulent sputum but no clinical and radiographic evidence of consolidation, after sputum has been obtained of microscopy and culture, should be treated with simple oral antibiotic against Streptococcus pneumoniae and Haemophilus infuluenze, such as amoxicillin and clavulanic acid, second generation cephalosporin or macrolide (the interaction of macrolide with cyclosporine should be remembered).

b. The patient with fever and radiographic changes requires more searching review and careful management. Computed tomography scan of the lung often refines the morphology of the pulmonary lesion. CT is particularly useful when the chest

radiograph is negative or when the radiographic findings are subtle or non-specific. It is also essential to the definition of the extent of the disease process and the selection of it provides (a) useful diagnostic clues and (b) a valuable guide to the best technique for invasive pulmonary samplings if needed.

1. A febrile illness of abrupt onset (course <48 hours) with dominantly local of lobar shadowing on chest radiograph and CT scan strongly suggest bacterial pneumonia. With the likelihood of such aggressive and rapidly multiplying organisms, it is appropriate to start intravenous antibiotic treatment promptly after taking simple samples (blood, natural or hypertonic saline aerosol - induced sputum) for expert microbiology. The initial antibiotic regimen should be broad spectrum and cover Pneumococcus, Staphyloccus, Legionella and Pseudomonas. One possible regimen is a combination of cefuroxime, erythromycin and high doses of daily gentamicin.

2. For other patients in whom the pace of the disease is less acute or the chest radiograph shows more diffuse or scattered change, the differential diagnosis enlarges. A

determined investigation to produce a precise microbiological diagnosis predicts the best outcome, and CT scan is valuable in planning this.

a. Sputum, either natural or induced by aerosolized hypertonic saline[11] should be obtained if possible. Expert assessment of the sputum sample by fluorescent stains for mycobacteria, of DNA amplification (polymerase chain reaction) for Pneumocystis[12] may obviate the need for invasive samplings.

b. If sputum is unavailable or non-diagnostic, invasive sampling is appropriate. Invasive sampling improves diagnostic yield and clinical outcome, through application of precise effective medication.

Alveolar lavage taken by fiberoptic bronchoscopy is appropriate when the CT scan or radiograph shows diffuse or alveolar pattern changes. Some authors favour concurrent transbronchial biopsies per bronchoscope, but this poses increased risk of pneumothorax and hemorrhage, and in bronchial lavage alone provides diagnostic yields greater than 75%[14,15]. Who1e array

of diagnostic techniques can be applied readily to the liquid sample, including microscopy after histo-chemical and immuno-fluorescent stains, solid-phase immuno-assays (enzyme-linked immuno-sorbent assays) for microbial antigens and microbe-specific DNA amplifications[13].

Trans-thoracic or percutaneous fine-needle aspiration of pulmonary material is more appropriate when CT scan shows localized, nodular lesions (with or without cavitation, although diagnostic yields appear higher when cavitation is present)[2]. Guidance of the needle by CT scan is optimal, and the same microbiological procedures can be applied to the sample as to the alveolar lavage, although less material is available. The use of modern 22- or 23-gauge needles minimizes risk of pneumothorax or bleeding; pneumothorax problems may be minimized by placing the patient with the sampled lung dependent for 1 hour post-procedure[16].

Formal lung biopsy is appropriate when a patient with pneumonitis is declining, and there is still not a secure diagnosis.

Open-lung biopsy is diagnostically effective but traumatic and usually demands post-procedure automatic ventilation.

Thoracoscopic lung biopsy, if available, offers a less invasive procedure that is appropriate for diffuse or peripheral lung lesions[17].

Treatment in this group of patients should be dictated by the diagnostic findings. P. carinii is treated with co-trimoxazole intravenously or orally in a dosage of 15 or 20 mg/kg/d of trim ethoprim and 75 or 100 mg/kg/d of sulfamethoxazole divided into two to four doses. If severe renal failure is present, the dosages are dictated by measuring free sulfa levels, aiming for values between 100 and 150 pg/ml, or trimethoprim levels, aiming for values between 3 and 5 pg/ ml. In moderate renal impairment (creatinine clearance 15-30 ml / mm), a standard dosage generally can be used for 3 days followed by a 50% dosage, but plasma levels should be tested. In all cases, treatment should continue for 2 weeks, and it seems rational to maintain the patient on chemoprophylaxis with co-trimoxazole, 480 mg twice daily by mouth[9] until the dosages of immuno - suppressives have been reduced in the longer term. Response to treatment is good (>80%) when the diagnosis is made early, but some patients need temporary cessation or reduction of immunosuppressives to allow recovery from Pneumocystis pneumonia. Hypersensitivity to co-trimoxazole with rash or fever is the indication for a change of treatment (eg., pentamidine, 4 mg / k /

d by intravenous infusion over 1 hour)[18]. Chemoprophylaxis with pentamidine can be administered effectively as an inhaled preparation, 300 mg monthly[19] from a suitable nebulizer device.

Aspergillus pneumonia demands prompt and vigorous treatment with amphotericin[20]. Liposomal formulations of amphotericin are considerably less nephrotoxic and probably of comparable efficacy, although they have not been formally evaluated in this setting. Nocardia is treated best with a sulfonamide such as sulfadiazine. Four to six divided doses of sulfadiazine daily may be needed as well as monitoring of serum levels (target, 100-150 rig/ml); treatment may need to be prolonged for many weeks after clinical resolution to prevent relapse.

The treatment of tuberculosis can be complicated by the influence of renal function on anti-tuberculous drug excretion (e.g., ethambutol) and by the influence of rifampicin on the metabolism of other drugs (e.g., cyclosporine;). In the treatment of established disease, the use of rifampicin, isoniazid and pyrazinamide in combination (none of whose levels are influenced seriously by impaired renal function) offers an appropriate regimen. After 2 months of triple chemotherapy, rifampicin and isoniazid can be

continued for 4 more months. Easing of immunosuppressive regimens may be needed to ensure recovery.

Respiratory failure (arterial oxygen tension <8 kPa or 60 mmHg) is treated with simple oxygen supplementation (30-40%). Exhaustion or worsening blood gases frequently leads to the need for ventilation. Some patients with acute syndromes may be incubated and ventilated before diagnostic bronchoscopy is undertaken. Many patients recover despite the need for temporary ventilation.

FOCAL / SEGMENTAL INFILTRATES

Acute Infiltrates

- Consider noninfectious mimics of pneumonia
- Workup for presumed bacterial pneumonia same as normal host

Diagnostic tests:

- Sputum Gram Stain / culture
- Blood Cultures
- LFTs
- Legionella DFA
- Legionella IFA (serology)

Subacute / Chronic Infiltrates

- Consider Aspergillus, Nocardia, Cryptococcus

Diagnostic tests :

- Trans Bronchial Biopsy or open lung biopsy

DIFFUSE INFILTRATES

Acute Infiltrates

- Consider non-infectious mimics of pneumonia
- Pneumocystis carinii pneumonia

Diagnostic tests:

- Serum LDH
- Arterial blood gases
- Gallium Scan

Subacute / Chronic Infiltrates

- Consider CMV/ RSV pneumonia

Diagnostic Tests:

- Arterial blood gases
- Gallium lung scan
- Culture viral respiratory secretions for CMV, RSV

CHARACTERISTIC PATTERNS OF PULMONARY INFILTRATES

The appearance of the infiltrates on the chest radiograph provides important information on diagnostic possibilities. For example, diffuse infiltrates may suggest pulmonary haemorrhage, leukoagglutinin reactions mimicking pneumonia, acute respiratory distress syndrome (ARDS), and CHF. Infectious causes of diffuse infiltrates in compromised hosts include viral pneumonias and PCP.

Focal infiltrates suggests bacterial pneumonia, particularly if presenting acutely, but focal infiltrates presenting subacutely or chronically should suggest Aspergillus, Nocardia, or Cryptococcal infection. Multifocal infiltrates suggest Legionella, Nocardia, Aspergillus, or TB. Rapidly progressive asymmetrical infiltrates in a patient with CAP should suggest the possibility of Legionnaires' disease.

Nodularity suggest Legionella, particularly Legionella micdadei, S. aureus pneumonia, or N. asteroids. Multifocal infiltrates are usually caused by Nocardial or fungi, particularly Aspergillus or Cryptococcus but does not occur as a solitary entity in compromised hosts. Candida occurs only as part of multiorgan involvement in disseminated candidal infection.

Peribronchial infiltrates suggest heart failure in a patient without chronic bronchitis or among the infectious agents, viral pneumonias, or PCP. A perihilar intersititial pneumonia with a increase in peribronchial markings has the same differential Diagnosis (eg., CHF, PCP, or viral pneumonia (eg., CMV).

The appearance of consolidation on the chest radiograph should suggest bacterial pneumonia, pulmonary emboli or infarction, or uncommonly CHF. Consolidation also is a feature of fungal pneumonias and Nocardia, but rarely is a feature of viral pneumonias. Cavitation is another radiologic sign that if present should suggest Aspergillus, Nocardia, or a bacterial necrotizing pneumonia caused by K. pueumoniae or S. aureus.

The diffuse infiltrates on the chest radiograph further may be divided into two clinical categories depending upon the degree of

hypoxemia. Patients with extensive pulmonary infiltrates and a normal or near normal A-a2 gradient, without severe hypoxemia, have lung lesion usually caused by CHF or a pulmonary haemorrhage. Alternately, a large A-a2 gradient or severe hypoxemia does not accompany Aspergillus, Nocardia, Cryptococcus, or bacterial infections even with extensive pulmonary infiltrates. In contrast, diffuse pulmonary infiltrates with hypoxemia suggest an interstitial oxygen diffusion defect and are typical of viral pneumonias (e.g., CMV, adenovirus, influenza, respiratory syncytial virus [RSV or PCP)

	Nodular	***Perithilar***	***Multifocal***	***Consolidation***	***Cavitation***
Acute Infiltrates	Legionella	CHF PCP	Legionella CHF Pulmonary emboli	Bacterial Pneumonia Pulmonary infarct CHF	Pseudomonas aeruginosa Klebsiella Staphylococcus aureus
Subacute /Chronic infiltrates	Aspergillus Nocardia Cryptococcus	RSV CMV Cryptococcus	Aspergillus Nocardia TB/MAI	Aspergillus Nocardia Cryptococcus Carcinoma	Nocardia Aspergillus Anaerobic lung abscess TB/MAI

RESULTS

Total No. of Renal transplant patients in the study period (n) = 267

Total episodes of lung infections = 64 (23.97%)

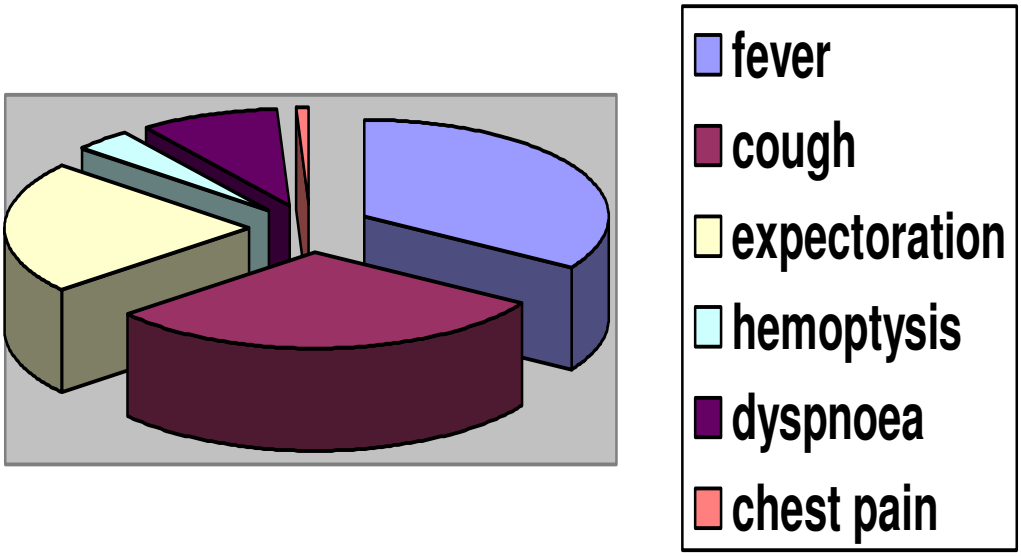
Age group varied between 17 to 50 years .Mean age- 31 yrs ± 8.8

Sex distribution

Males 49/64 (76.56 %)

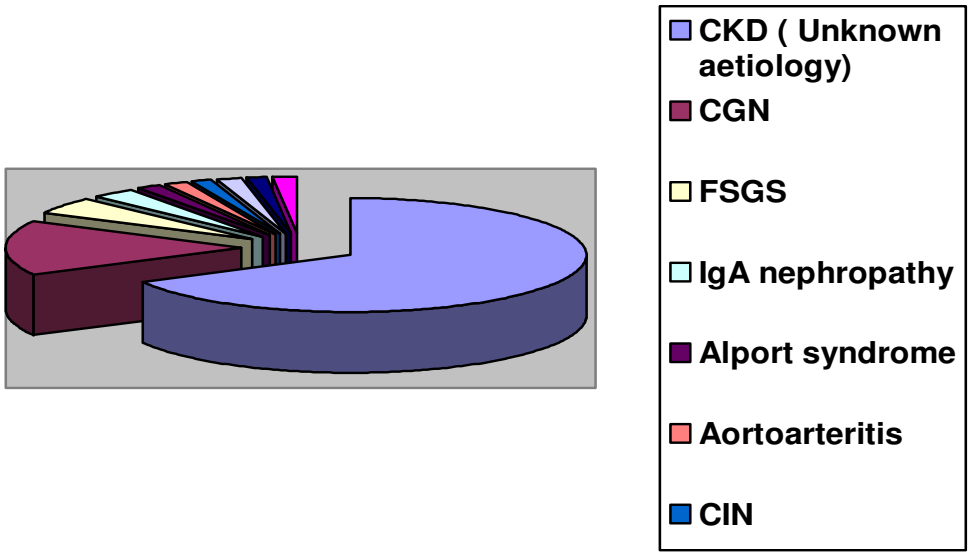
Females 15/64 (23.43%)

Clinical profile:



No	*Clinical Features*	*Incidence (n) = 64*	*%*
1.	Fever	44	68.75
2.	Non productive cough	39	60.93
3.	Expectoration	29	45.31
4.	Hemoptysis	5	7.8
5.	Exertional dyspnoea	12	18.75
6.	Chest pain	1	1.56

BASIC DISEASE

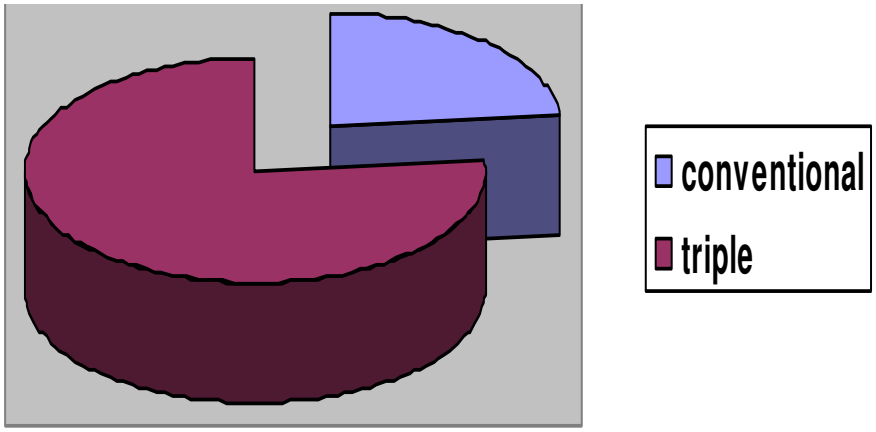


DONORS

No	*Donors*	*Number*	*%*
1.	First degree relatives	61	95.3%
2.	Second degree relatives	3	4.68%

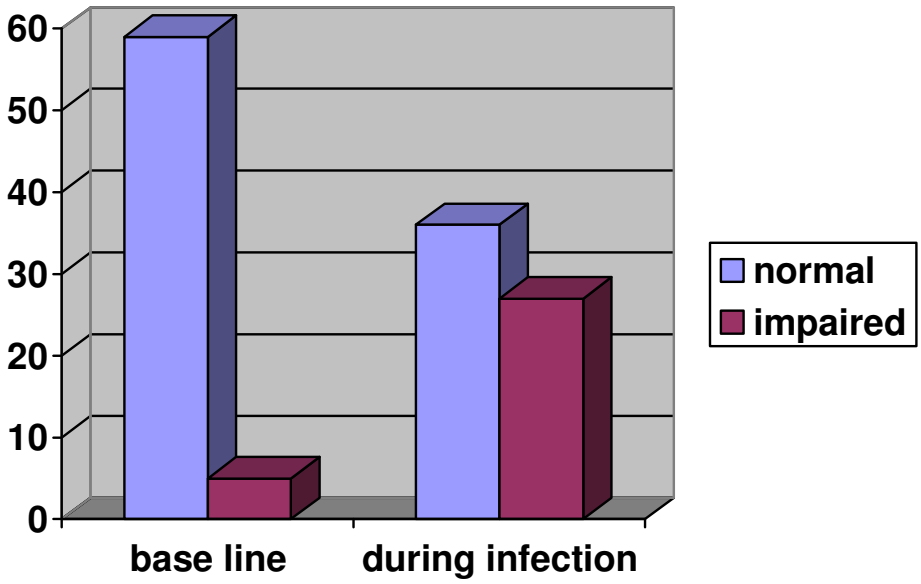
No	*Basic disease*	*Incidence (n)= 64*	*%*
1.	CKD (Unknown aetiology)	43	67.18%
2.	CGN	10	15.62%
3.	FSGS	3	4.68%
4.	IgA nephropathy	2	3.12%
5.	Alport syndrome	1	1.56%
6.	Aortoarteritis	1	1.56%
7.	Chronic interstitial disease	1	1.56%
8.	Diabetic nephropathy	1	1.56%
9.	Reflux nephropathy	1	1.56%
10.	Vasculitis	1	1.56%

IMMUNOSUPPRESSION



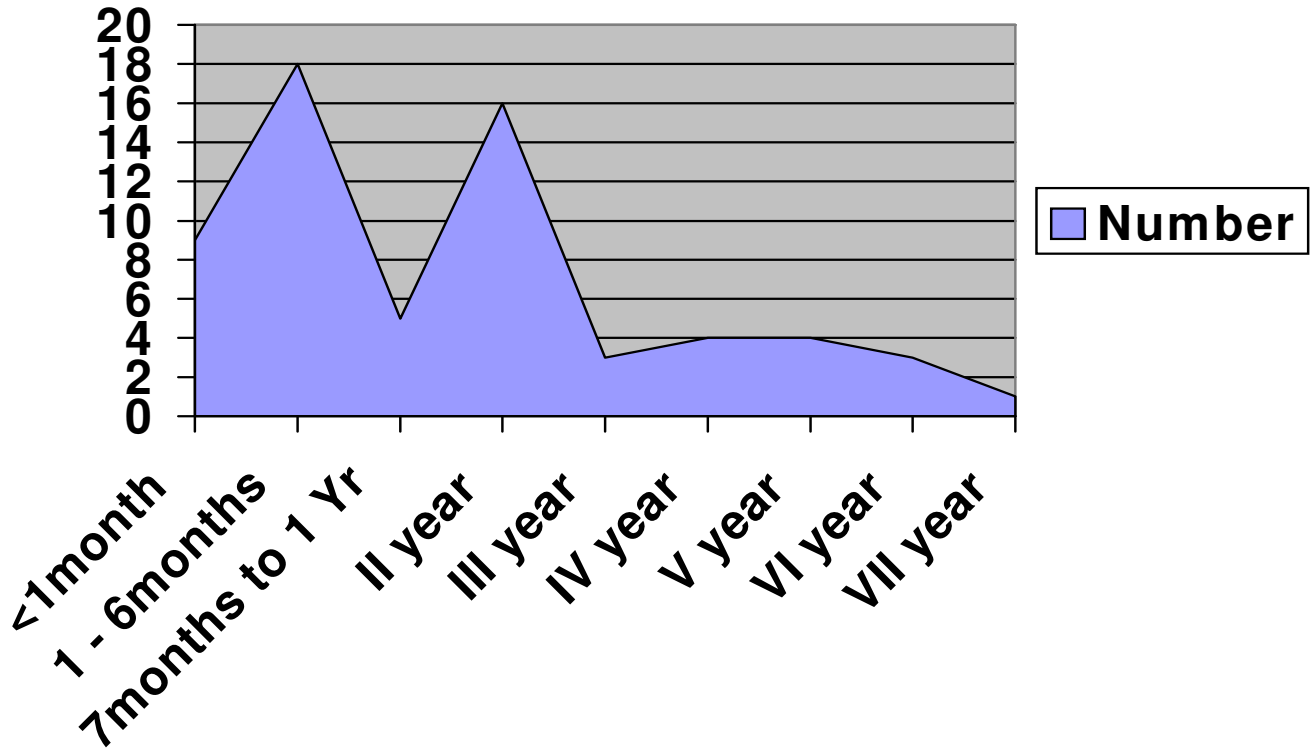
No	*Immunosuppression*	*Number*	*%*
1.	Conventional (Azathioprine + Prednisolone)	15	23.43%
2.	Triple (CsA+ Azathioprine + prednisolone)	49	76.56%

GRAFT FUNCTION DURING THE INFECTION



Graft function	*Normal*	*Impaired*
Base line	59 (92.18%)	5 (7.81%)
During infection	36 (56.25%)	27 (42.18%)

TIME AT WHICH THE INFECTION OCCURRED



Period	***Number (%)***	***Organism grown***
<1month	9 (14.06%)	Klebsiella 5 (55.55%)
		Coagulase negative staphylococci 1 (11.1%)
		Pseudomonas 1(11.1%)
		Unidentified 2 (22.2%)

Period	***Number (%)***	***Organism grown***
1 – 6 months	18 (28.12%)	Tuberculosis 7(38.8%)
		Polymicrobial 5 (27.77%)
		Pseudomonas 5 (27.77%)
		Klebsiella 3 (16.66%)
		Atypical Mycobacteria 2 (11.1%)
		Acinetobacter 1 (5.5%)
		Enterococci 1 (5.5%)
		Staphylococci 1 (5.5%)
		Candida 1 (5.5%)
		Unidentified Organism 3 (16.66%)

Period	***Number (%)***	***Organism grown***
6 months – 1 year	5 (7.81%)	Tuberculosis 2 (40%)
		Klebsiella 1 (20%)
		S. aureas 1 (20%)
		Candida 1 (20%)
		Pseudomonas 1 (20%)
		Unidentified Organism 1 (20%)

Period	*Number (%)*	*Organism grown*
1-2 years	16 (25%)	Tuberculosis 4 (25%)
		Klebsiella 3 (18.75%)
		Pseudomonas 2 (12.5%)
		Mucor 2 (12.5%)
		Candida 2 (12.5%)
		Polymicrobial 2 (12.5%)
		Unidentified Organism 3 (18.75%)

Period	*Number (%)*	*Organism grown*
> 2years	16 (25%)	Tuberculosis 7 (43.75%)
		Klebsiella 5 (31.25%)
		Poly microbial 4 (25%)
		Pseudomonas 2 (12.5%)
		Candida 2 (12.5%)
		Atypical mycobacteria 1 (6.25%)
		E. Coli 1 (6.5%)
		Staphylococcus 1 (6.25%)
		Streptococcus 1 (6.25%)

RISK FACTOR ANALYSIS FOR THE ENTIRE COHORT

Risk Factors	*Incidence*	*%*
Leucopenia	35	54.68%
ART	26	40.63%
CMV	13	20.31%
PTDM	12	18.75%
HCV	8	12.5%

SENSITIVITY OF SPUTUM STAIN VS. CULTURE

	Sputum stain	***Sputum Cult/ Sens***
Positive	15 (24.43%)	10 (15.62%)
Negative	49 (76.56%)	54 (84.37%)

SENSITIVITY OF SPUTUM VS. BAL ANALYSIS

	Sputum stain	***BAL***
Positive	23/ 64 (35.93%)	18/18 (100%)
Negative	41 (64.06%)	0/18 (0%)

SENSITIVITY OF IMAGING STUDIES

	X ray chest	***CT chest***
Positive	51/64 (79.69%)	24/29 (82.76%)
Negative	13/64 (20.31%)	5/29 (17.24%)

NON TUBERCULOUS BACTERIAL INFECTIONS

Total No. of nontuberculous bacterial infections - 14

Clinical profile:

No.	***Clinical features***	***Incidence (n) = 14***	***%***
1.	Fever	10	71.42%
2.	Cough	10	71.42%
3.	Expectoration	8	51.02%
4.	Exertional dyspnoea	3	21.42%
5.	Hemoptysis	3	21.42%
6.	Chest pain	0	0

TIME AT WHICH THE INFECTION OCCURRED :

Period	***Number (%)***	***Organism grown***
<1month	4 (28.57%)	Klebsiella 3 (75%)
		CONS 1 (25%)
2 – 6 months	2(14.28%)	Pseudomonas 2 (100%)
6 months – 1 year	1(7.14%)	Klebsiella 1 (100%)
1-2 years	5(35.71%)	Klebsiella 3 (60%)
		Pseudomonas 2 (40%)
> 2years	2 (14.28%)	Klebsiella 2 (100%)

RISK FACTOR ANALYSIS FOR THE BACTERIAL COHORT:

Risk factors	***Incidence***	***%***
Leucopenia	9	64.28
ART	5	35.71
CMV	4	28.57
PTDM	2	14.28
HCV	2	14.28

TUBERCULOSIS

Number of patients with tuberculosis:

Microbiologically proven	3 (20.31%)
Empirical ATT	9 (14.06%)
Total	22 (34.37%)

Incidence of tuberculosis with respect to entire cohort: 22/247 (8.9%)

No	***Clinical Features***	***Incidence n = 13***	***%***
1.	Fever	13	100
2.	Cough	13	100
3.	Expectoration	10	76.92
4.	Hemoptysis	4	30.76
5.	Exertional dyspnoea	4	30.76
6.	Chest pain	0	0

IMAGING PATTERN

No	***Clinical features***	***Chest Xray***	***%***	***CT Chest***	***%***
1	Normal	2	15.38	0	0
2	Unilateral, focal	7	53.84	5	38.46
3	Diffuse	4	30.76	2	15.38
4	Not done	0	0	6	46.15

DIAGNOSTIC METHODOLOGY

Sputum AFB stain	5
BAL AFB	5
BAL mycobacterial culture	3

TIME OF OCCURRENCE

S. No	***Period***	***Number***	***%***
1.	2-6 months	2	15.38
2.	7- 12 months	2	15.38
3.	13 – 24 months	2	15.38
4.	> 2 years	7	53.84

RISK FACTOR ANALYSIS

Risk factors	***Incidence***	***%***	***For the entire cohort %***
Leucopenia	7	53.84	54.68%
ART	5	38.46	40.63%
CMV	4	30.76	20.31%
PTDM	4	30.76	18.75%
HCV	2	15.38	12.5%

ATYPICAL MYCOBACTERIA

Total No. of atypical mycobacterial lesions identified - 3

Sputum negative in all 3 of them

DIAGNOSTIC METHODOLOGY

Sputum positive 0

BAL AFB Positive 3

BAL culture Positive 3

CLINICAL PROFILE

No.	***Clinical features***	***Incidence (n)= 3***	***%***
1.	Fever	0	0
2.	Cough	0	0
3.	Expectoration	0	0
4.	Hemoptysis	0	0
5.	Exertional dyspnoea	0	0
6.	Chest pain	0	0
7.	Vague ill health	3	100

TIME OF OCCURRENCE

S.No	***Period***	***Number***	***%***
1	2-6 months	0	0
2	7- 12 months	0	0
3	13 – 24 months	2	66.66
4	> 2 years	1	33.33

IMAGING

No	*Clinical Features*	*Chest Xray*	*%*	*CT chest*	*%*
1	Normal	0		0	0
2	Unilateral, focal	0		0	0
3	Diffuse	3	100	3	100

RISK FACTOR ANALYSIS

Risk factor s	*Incidence*	*%*
Leucopenia	2	66.66
ART	2	66.66
HCV	1	66.66
PTDM	1	33.33
CMV	1	33.33

FUNGAL INFECTIONS

Total No. of fungal lesions identified 8

Diagnostic methodology

Sputum KOH 1

Sputum Culture 1

BAL KOH 1

BAL culture 4

CT guided biopsy 1

CLINICAL PROFILE

No.	***Clinical features***	***Incidence (n)=8***	***%***
1	Fever	6	80
2	Cough	5	62.5
3	Expectoration	3	37.50
4	Exertional dyspnoea	4	50
5	Hemoptysis	1	12.5
6.	Chest pain	1	12.5

TIME OF OCCURRENCE

S.No	*Period*	*Number*	*%*
1	2-6 months	2	20
2	7- 12 months	0	0
3	13 – 24 months	4	50
4	> 2 years	2	20

IMAGING

No.	*Clinical features*	*Chest X-ray*	*%*	*CT chest*	*%*
1	Normal	1	12.5	1	12.5
2	Unilateral, focal	1	12.5	1	12.5
3	Diffuse	6	75	6	75

RISK FACTOR ANALYSIS

Risk Factors	*Incidence*	*%*	*For the entire cohort %*
Leucopenia	6	80	54.68%
ART	5	62.5	40.63%
HCV	2	20	20.31%
CMV	2	20	18.75%
PTDM	1	12.5	12.5%

FUNGAL SPECIES IDENTIFIED:

Species	*Incidence (number)*	*%*
Mucor	2	25%
Candida	6	75%

POLYMICROBIAL INFECTIONS

These are defined as infections with more than 1 organism.

Total no. of polymicrobial infections - 17 / 64 (26%)

Clinical profile:

No.	***Clinical features***	***Incidence n= 17***	***%***
1	Fever	12	70.58%
2	Cough	12	70.58%
3	Expectoration	6	35.29%
4	Exertional dyspnoea	7	41.17%
5	Hemoptysis	2	11.76%
6.	Chest pain	0	0

TIME AT WHICH THE INFECTION OCCURRED

Period	***Number (%)***	***Organism grown***
<1month	3 (17.64%)	Bacterial 2
		Fungal + bacteria 1
1 – 6 months	5 (29.41%)	Tuberculous + nontuberculous 4
		Fungal + bacterial 1
6 months – 1 year	0	
1-2 years	3 (17.64%)	Tuberculous+ nontuberculous 2
		Fungal+ bacterial 1
> 2years	6 (35.29%)	Bacterial 2
		Tuberculous+ nontuberculous 2
		Tuberculous+ nontuberculous + fungal 2

RISK FACTOR ANALYSIS FOR THE MIX INFECTIONS:

Risk factors	***Incidence***	***%***	***For the entire cohort %***
Leucopenia	8	47.05%	54.68%
ART	8	47.05%	40.63%
CMV	3	17.64%	20.31%
PTDM	4	23.52%	18.75%
HCV	3	17.64%	12.5%

DISCUSSION

267 patients who received living related renal allografts between 2000 and 2006 were included in the study.

Pulmonary infection is the most common tissue invasive infection observed in transplant recipients2. In our study it was noted in 23.97%.

The age group was distributed 17 to 50 years, the mean age being 31± 8.8 years. There was a male predominance 49/64 (76.56%).

Fever was the commonest symptom amounting to 68.75%, followed by cough that was seen in 60.93 %.

The cough was nonproductive in 15.63% and productive in 45.31 %. Exertional dyspnoea and hemoptysis were observed in 18.75 % each.

In immunosuppressive individuals symptoms can be vague and delayed[1]. 17/64 (26.56%) patients presented with nonspecific vague ill health. They did not have any symptoms pertaining to pulmonary infection which is known to happen in immunosuppressed individuals.

The aetiology of CKD was unknown in majority (67.18%) of our patients. These individuals presented with bilateral contracted kidneys and severe renal failure. Presumed CGN was observed in 15.62%. CGN was presumed by the presence of proteinuria, hypertension and edema. Globally, diabetes is the common cause of ESRD. But only one had diabetic ESRD in our study. This is because diabetic patients have difficulty in finding a nondiabetic live related (first degree) donor.

The centre considers only related transplantation; 95.3% of donors were first degree relatives.

Majority (76.56%) of the patients were on triple (cyclosporine + azathioprine + prednisolone) immunosuppression . The transplant unit has a policy of withdrawing cyclosporine for patients with stable graft function at the end of first year .

To avoid rebound rejection we practice overlapping steroids during withdrawal period. This is bound to add to the total immunosuppressive dose. It also necessitated analyzing infections separately during the hike i.e. between 12 – 24 months.

GRAFT FUNCTION AT BASE LINE AND DURING INFECTION

Any infection including respiratory infection is a cause of graft dysfunction. 7.81% had graft dysfunction before LRTI. It increased to 42.18% once lung infection was set in.

TIME AT WHICH THE INFECTION OCCURRED

The time table of infective complications developed by Rubin et al[2]. is adopted for our analysis. viz.

1). 0-4 weeks in which routine infections of wound, lines and hospital infections are expected.

2). 2- 6 months, where the immunosuppression is the maximum and opportunistic infections are common.

3). 6-12 months where routine infections are expected as the immunosuppressive dose is toned down

4). 12 - 24 months, this period is peculiar to our center as we hike steroids during calcineurin inhibitor withdrawal where again opportunistic infections are expected.

OUR Cs A WITHDRAWAL PROTOCOL

Time	***CsA***	***Azathioprine***	***Prednisolone***
- 2weeks	4mg / kg	1.5mg/kg	30mg/day
-1 week	4mg / kg	2.5mg/kg	30mg/day
0	2.7 mg / kg	2.5mg/kg	30mg/day
4 weeks	1.3 mg / kg	2.5mg/kg	30mg/day
8 weeks	Stop	2.5mg/kg	30mg/day
12 weeks	Nil	2.5mg/kg	25 mg/day
16 weeks	Nil	2.5mg/kg	20 mg/day
20 weeks	Nil	2.5mg/kg	15 mg/day
24 weeks	Nil	2.5mg/kg	10 mg/day
After 24 weeks	nil	2.5mg/kg	10 mg/day

About 14.06%, 28.12%, 7.81%, 25%, and 25% of lung infections occurred at <1month, between 1to 6 months, between 6 months to 1 year, between 1 to 2 years and >2 years respectively. Maximum number of infections occurred between 2 and 6 months when the dose of immunosuppression was at its maximum. Least number of infections occurred between 6 months and 1 year and

after 2 years when the dose of immunosuppression was at its lowest. This is in concordance with other studies [2]. [30]. There is a second peak of infections in the second year which we attribute to steroid hike during CsA withdrawal.

MICROBIOLOGY WITH RESPECT TO POST TRANSPLANT DURATION

< 1month:

Klebsiella (55.55%) was the commonest cause of lung infection during this period, followed by Pseudomonas (11.1%). These are the commonest cause of Nosocomial infections in our hospital (Personal communication: Microbiology department). This is in concordance with previous experiences by various authors. Infections like tuberculosis and fungal infections were not seen.

2- 6 months:

Tuberculosis (38.8%) was the most frequent infection encountered in this period. Fungal infections (11%) like Candida were noted during this period.

6 Months to 1 Year:

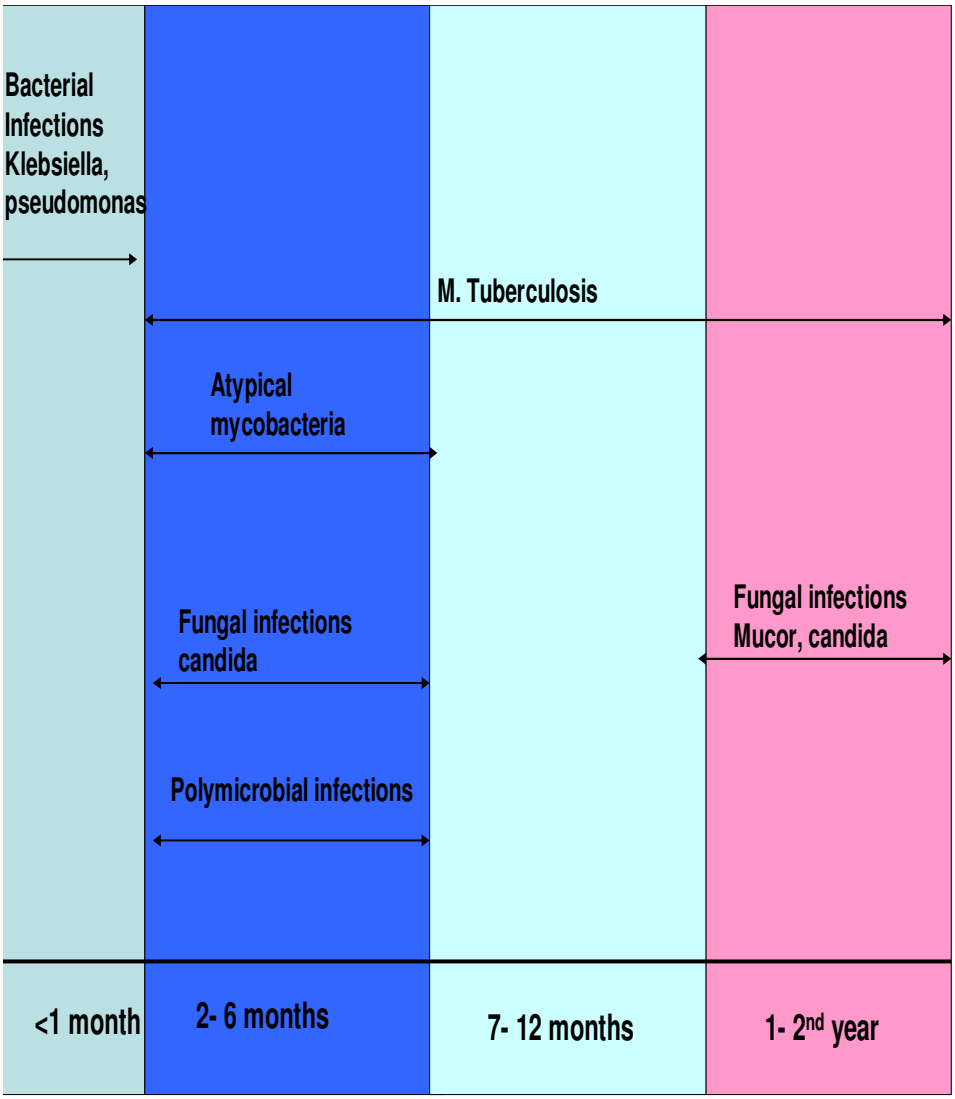
Again tuberculosis (40%) was noted to be the commonest. In our part of world tuberculosis can behave both as opportunistic infection as well as endogenous reactivation or denovo community acquired infection.

1- 2 years

Tuberculosis remains the commonest infection in this period but fungal infections like Candida and Mucor again appear in this period of time This reflects intense immunosuppression during CsA withdrawal. It is appropriate to reevaluate the current CsA withdrawal protocol and to consider reducing steroid dose[28]

> 2 years

The commonest infection noted during the entire 2nd to subsequent 5th year is tuberculosis, reflecting significant exposure of our transplant recipients to this bacilli; there may be a case for more aggressive screening for tuberculosis both pre and post transplant as well as for considering INH prophylaxis.



Time Table for Post Transplant Pulmonary Infections.

RISK FACTORS FOR DEVELOPING POST TRANSPLANT PULMONARY INFECTION

Two factors, leucopenia and anti rejection therapy (ART), that reflects intensity of immunosuppression and two other immunomodulating viral infections, CMV and HCV, that has a bearing on other infections were considered. The other factor considered was the post transplant diabetes mellitus.

1.LEUCOPENIA

Leucopenia happens with bone marrow suppression as it can occur as a adverse effect of azathioprine in a dose dependent fashion. Such bone marrow suppression also occurs with CMV infection.

It was seen in more than half (54.68%) of individuals with lung infections. Moreover it is a risk factor for mortality. Both the patients who died during the acute infection had leucopenia.

2. ART:

In our center ART consists of inj. Methyl prednisolone 15mg / Kg/ day for 3 days. We extend it by 2 more days if the serum creatinine was found to be persistently high. Such treatment adds significantly to the net immunosuppression and predisposes to

opportunistic infections. It was seen in as high as 40. 63 % in patients with lung infections.

3. CMV

The relationship between CMV and other infections is complex. The alloantigen expression is increased in the presence of CMV infection contributing to acute rejection which will necessitate more ART leading to more opportunistic infections. Moreover CMV infection is associated with bone marrow suppression. It was seen with 20.31% in our study.

4. HCV

HCV is an immunomodulating virus. Patients infected with HCV are considered for transplant when there is no sign of active hepatitis. They are offered transplantation if they have no signs of decompensated liver disease. The outcome of such transplant recipients is comparable with that of non-HCV recipients but for increased incidence of other infections in the first four months period. It was seen in 12.5 % of the study subjects.

5. PTDM

PTDM is defined as fasting sugar of >126mg/dl or post prandial sugar of >180 mg/dl in a patient, with normal glucose pretransplant. It has been associated with increased incidence and mortality of infective complications. It has been noted in 18.75% of our patients.

SENSITIVITY OF SPUTUM STAINING VS. CULTURE/ SENSITIVITY

Though sputum staining (Gram stain, KOH mount and AFB put together) is positive in 24.43% vs.15.62% on comparing with culture , it was not statistically significant.

SENSITIVITY OF SPUTUM ANALYSIS VS BAL

Sputum analysis (culture and staining put together) was less sensitive than BAL analysis (35.93% vs100%) [p< 0.001.Z= 4.54 95% CI 64% (49 – 79)] BAL though more invasive gave the microbiological diagnosis in all the occasions whenever it was done.

SENSITIVITY OF IMAGING MODALITIES

CT chest is slightly more sensitive than X-ray chest numerically (79.69% vs.82.76%) but not statistically significant. X-ray was normal in 20.31% whereas CT chest was normal in (17.24%)

NON TUBERCULOUS BACTERIAL INFECTIONS

Bacterial infections other than tuberculosis amounted to 14/64 (21.87%) of all infections.

Fever and cough were the commonest symptoms amounting 71.42% each.Dyspnoea and hemoptysis were seen in 21.42%.

Non tuberculous bacterial infections had a bimodal timing of occurrence, first one between 1 and 2 years (35.71%) and the second one in the first month (28.57%). Infections were least frequent (7.14 %) between 7^{th} -12^{th} month when the immunosuppression was at its minimum.

MICROBIOLOGY OF INFECTIONS

1. < 1month:

Klebsiella (75%) was the commonest cause of lung infection during this period.

This is the commonest cause of nosocomial infection in our hospital (personal communication: microbiology department).

2. Between 1 and 2 years:

Klebsiella was identified to be the commonest (60%) pathogen identified followed by Pseudomonas (40%).

ANALYZING THE RISK FACTORS

Leucopenia, ART, CMV, PTDM and HCV were noted in 64.28%, 35.71%, 28.57%, 14.28%, and 14.28% respectively

TUBERCULOSIS

Incidence of tuberculosis in the post transplant period has been documented to 5.7% to 10 %[4] in various studies. In our study, it was found to be (8.9%)

Number of patients with tuberculosis:

Microbiologically proven	13 (20.31%)
Empirical ATT	9 (14.06%)
Total	22 (34.37%)

For analysis purpose, microbiologically proven cases alone was considered.

Fever and cough was most frequent and encountered in all cases. Cough was productive in 76.92%. Hemoptysis and dyspnoea noted in 30.76%. There were no asymptomatic cases.

The chest X-ray showed focal disease in the majority(53.84%).; multifocal in 30.76%. Notably chest X-ray was normal in 15.38%.CT chest is sensitive and all were abnormal in patients with tuberculosis.

Sputum AFB yielded the diagnosis in only 38.46%. The other 61.5 % required BAL studies to diagnose the infection. In a significant 23 .07% of them only BAL Mycobacterial culture clinched the diagnosis reflecting that an aggressive approach is required to get the microbiological diagnosis.

Tuberculosis is the most common lung infection noted in any time window apart from the first month. It does not follow any particular time sequence of the Rubin's timetable. It is distributed in 15.38% in each of the 2^{nd} to 6^{th} month, between 6 and 12 months and between 1^{st} and 2^{nd} year.

Leucopenia was noted in 53.84%, ART in 38.46%, HCV in 15.4%. CMV infection (30.76%) and PTDM (30.76%) are more common in tuberculosis group but not found to be statistically significant.

TREATMENT

All of them recovered with ATT (INH, Rifampicin, Ethambutol, Pyrazinamide) which was given for a period of 18 months.

NON MYCOBACTERIAL INFECTIONS (NTM)

Atypical Mycobacterial infections were rare occurring in 4.69%.

All three did not have any symptoms pertaining to respiratory system. They did not have fever or cough/ expectoration. They were evaluated for vague illhealth.

Chest X ray and CT chest revealed diffuse lesions in all 3 of them.

Sputum was negative in all three of them

BAL AFB and culture was positive in all three.

Of the more than 90 known species of NTM, about one third have been associated with disease in humans[31]. The species we identified in our study was M.TB fortuitum chelonei;

2 of the infections occurred during the second peak of immunosuppression; 1 occurred after 2 years.

Leucopenia and ART was seen in 2 of them. PTDM, CMV, HCV infection are seen in 1 each.

All three of them improved with appropriate sensitive drugs (Ofloxacin, Co-trimoxazole, Amikacin).

FUNGAL INFECTIONS

Total number of fungal infections is 8 amounting to 12.5% of total infections

Fever was the commonest symptom (80%) followed by Cough which was seen in 62.5%. one had chest pain who had peripheral pulmonary nodule and had mucor infection.

80% had multifocal, diffuse lesions. One had focal lesion. One had normal imaging including CT chest.

BAL culture maximum yield (50%).Sputum KOH and culture positive in only one instance. The peripheral nodule was diagnosed by CT guided biopsy (Mucor).

Maximum (50%) number of infections occurred in the second peak of immunosuppression i.e between 1^{st} and 2^{nd} year.

20 % occurred during the first peak i.e. between 2^{nd} and 6^{th} month.

Between 7^{th} month and 12^{th} month there was no fungal infection reflecting minimal immunosuppression.

Leucopenia was noted in as high as 80% of them. ART was seen in 62.5% of them. This is more frequent than the entire cohort but not found to be significantly significant.

CMV and HCV infection noted in 20 % each and PTDM in 12.5%.Candida was the commonest species (75%), followed by Mucor mycosis(25%).

All received amphotericin .One of them (Mucor with peripheral pulmonary nodule) was treated with lobectomy in addition to amphotericin and he survived. 2 (20%) of them died. Both of them had leucopenia. One had Mucor.

POLYMICROBIAL INFECTIONS

Poly microbial infections amounted to 26.56% of all infections.

Fever and cough were the commonest symptoms amounting 70.58%. Cough was productive in 35.29%. Hemoptysis is rare, seen in 11.76%

Polymicrobial bacterial infections were most frequent (29.41%) between the 2nd and 6th month, when the immunosuppression was at its maximum. As discussed above there were no such infections between 7th and 12th month. Between 1st and 2nd year, 17.64% such infections were noted.

PERIOD OF OCCURRENCE

1. <1month :

Polymicrobial bacterial infection was noted in 2 and bacterial + candidal infection noted in 1.

2. 2- 6 months:

M.TB mix with other bacterial infections was the commonest pattern noted in 4 of them. In 1 of them bacterial + fungal infection was documented

3. Between 1st and 2nd year :

M.TB mix with other bacterial infections was seen in 2. Fungal infection mix with other bacterial infection is seen in 1 of them.

4. After 2 years

M.TB is the commonest organism mix with other bacterial in 2 and mix with fungal in 2.

Leucopenia, ART, CMV, PTDM and HCV were noted in 47.05%, 47.05%, 17.64%, 23.52%, and 17.64% respectively. None of these factors are found to be statistically significant.

CONCLUSIONS

In our study pulmonary infections are a major cause of morbidity in renal transplant recipients and it occurred in 23.97% of our study population.

One fourth of patients with pulmonary infections had no respiratory symptoms.

Nosocomial infection with Klebsiella is the commonest cause of lung infection in the first post transplant month.

Maximum number of infections occurred between 2^{nd} and 6^{th} month when the dose of immunosuppression was at its maximum.

Steroid hike during CsA withdrawal is complicated by an unacceptable second peak of pulmonary infections caused by Tuberculosis and Candida..

Mycobacterium tuberculosis was the commonest cause of lung infection during all time periods except 1st month.

The sensitivity of sputum staining techniques was 24% only when compared with BAL which had a sensitivity of 100%

X ray chest is normal in one fifths of lung infections

Microbiological diagnosis of tuberculosis required BAL studies in two third of cases

Candidal infection was the commonest fungal infection and occurred with higher dose of steroids, between 1 and 2 years in our study.

Polymicrobial infections occurred in one fourth of lung infections and they were common between 2nd and 6th month.

BIBLIOGRAPHY

1. J. Cohen et al.-Infectious complications after Renal transplantation-Kidney transplantation-Principles and practice Peter.J.Morris-5th edition

2. Jay. A. Fishman,Robert. H. Rubin (1998)-Infection in Organ transplant recipients - N. Engl. J.Med; 338.24

3. George.T.John et al. (1996)-A Time table for infections after renal transplantation in the tropics. Transplantation;61;6

4. Vinay Sakhuja et al. (1996)-The high incidence of tuberculosis among renal transplant recipients in India-Transplantation 61;2;211-215

5. Fishman,J.A. and Rubin,R.H. (1998).Pneumonia in the organ transplant recipient. In Pulmonary Diseases and Disorders,3rd Ed,(J.A.fishman, et al, eds.) p.2153 Mc Graw-Hill,NewYork.

6. Hopkin,J.M.Turney,J.H.,Young,J.A.(1983).Rapid diagnosis of obscure pneumonia in immunosuppressed renal patients by cytology of alveolar fluid.Lancet 2,299.

7. Arduino,R.C.,Johnson,P.C. and Miranda, A.G (1993). Nocardiosis in renal transplant recipients. Clin. Infect. Dis. 16,505.

8. Morgan, J. S., Schaffner, W. and Stone, W. J. (1986). Opportunistic strongyloidiasis in renal transplant recipients. Transplantation 42,518.

9. Higgins,R.M.Bloom,S.L.,Hopkin,J.M.,Morris,P.J.(1988)Risks and benefits of cotrimoxazole prophylaxis for Pneumocystis pneumonia in renal transplantation. Transplantation, 47,558.

10. Yu,Y.L., Chow, W., Humphries, M.J., et al (1986). Cryptic miliary tuberculosis.Q.J.M.59,421.

11. Bigby, P. D., Margolskee, D. and Curtis, J. L. (1986). Usefulness of induced sputum in diagnosis of pneumonia in patients with AIDS. Am. Rev.Resp.Dis.133,515.

12. Wakefield, A. E., Miller, R.M., Guiver, L. and Hopkins, J. M. (1991) .DNA amplification for the diagnosis of Pneumocystis Pneumonia from induced sputum.

13. Kalin,M., Grandien,M., and Petrini,B..(1998). Laboratory diagnosis of respiratory infections,In infectious diseases of

the Respiratory tract,(M.Ellis,ed.),p.3.,Cambridge University Press,Cambridge.

14. Hopkin,J.M.(1991). Pneumocystic carinii p.1. Oxford University press, Oxford

15. Young,J.A. Hopkins J.M. and Cutherberston,W.P. (1984) Pulmonary infiltrates in immunocompromised patients:diagnosis by cytological examination of bronchoalveolar lavage fluid. J. Clin.Patho. 37,390

16. Moore, E. H., Shepard, J. O., MacLoud, T. C., et al (1990). Positional precautions in needle aspiration lung biopsy. Radiology 175,733.

17. Ferguson,P.E. and Landreneau,R.J. (1988). Thoacoscopic or Open lung Biopsy in the diagnosis of interstitial lung disease. Chest Surg. Clin. N. Am. 4,749

18. Haverkos,H.W. (1984) Assessment of therapy for Pneumocystis carinii pneumonia. Am. J.Med.,76,501.

19. Armstrong,D. and Bernard. E. (1991). Aerosol Pentamidine. Ann.Intern Med 109- 852

20. Denning, D.W. (1996). Therepeutic outcome in invasive aspergillosis. Clin. Infect.Dis.23,1147

21. Burke A Cunha. Pneumonias In The Compromised Host. Infectious disease clinics of North America. Volume 15, June 2001.

22. Rubin RH, Infections In The Organ Transplant Recipients Clinical Approach To Infection In The Compromised Host. 3rd ed. NewYork Plenum Publishing1994.624,705

23. Rubin RH, Infectious Diseases Complications Of Renal Transplantation.Kid. Int.1993, 44,321-336

24. Fishman JA Pneumocystis carinii And Parasitic Infections In Transplantations. Infect Dis clin.North Am 1995: 9, 1035-44

25. Hadley S Karchmer AW. Fungal infections in solid organ transplant recipients. Infect. Dis clin North Am 1995; 9,1045-74

26. Peterson. P.K. Ferguson R, Fryd D .S. et al Infectious Diseases In Hospitalised Renal Transplant Recipients: A prospective study of a complex and evolving problem. Medicine (Baltimore) 1982: 61, 360

27. Hiesse. C Kriaa F Eshwege P et al. Long terms results and risk factors of quadruple immunosuppression in renal transplantation. Transplant Proc. 1999:31, 1101

28. Morris et al. Low dose oral prednisolone in renal transplantation, Lancet 1982. 1,525.

29. John son et al Respiratory disease in Kidney and Liver Transplant Recipients. Respiratory diseases in immunosuppressed host. Philadelphia Lippincott. 1991. 567-94.

30. George T. John et al .A time table for infections after renal transplantation in the tropics. Tranplantation 1996; 61, 6

31. Katoch.V.M. Infections due to nontuberculous mycobacteria. Indian J Med Res Oct 2004.

32. Paulose P Thomas. Post transplant tuberculosis Editorial Saudi J Kidney Dis Transplant 2002: 13 (4) 445- 450

Name	Age	Sex	Month of TX	cr at dis	Fever	Cough	Boe	Hemopt	LRTI mth	Creat Infect	No. of AR	ART	PTDM	HCV	CMV	Leucop	Spgs	Sp KOH	Sp AFB	Sp C/S	BAL g-s	BAL-koh	BAL -afb	BAL C/S	Org
Ganesan	32	m	may 00	88	yes	nil	nil	nil	38	198	nil	yes	yes	nil	yes	nil	nil	nil	nil	nil	nil	nil	yes		tb
Arumugam	50	m	may 06	87	yes	nil	nil	nil	15	466	1	yes	no	nil	nil	yes	nil	yes	nil	nil	nil	yes	nil	yes	fu
Veeramani	37	m	oct 06	80	yes	nil	nil	nil	1	88	nil	nil		nil	nil	yes	gnb	nil	nil	nil	nil	nil	nil	nil	uk
Ganeshkumar	41	m	jul 06	90	yes	nil	nil	nil	1	96	nil	nil		nil	nil	nil	nil	nil	nil	nil	nil	nil	nil	nil	uk
Ramaswamy	25	m	nov 01	88	yes	yes	nil	nil	2	88	nil	nil	nil	nil	nil	yes	nil	nil	yes	nil	nil	nil	nil	nil	tb
Padmanaban	25	m	mar 02	88	yes	yes	nil	yes	48	422	nil	yes	yes	nil	nil	yes	nil	nil	nil	nil	g+cocci	yes	yes		tb
Nirmala	47	f	mar 00	88	nil	nil	nil	nil			nil	nil		nil	nil	nil	nil	nil	nil	nil	nil	nil	nil	nil	u.k
Gurupandian	40	m	jan 00	96	yes	yes	nil	nil	24	158	nil	yes	nil	nil	nil	yes	nil	nil	yes	nil	nil	nil	nil	nil	tb
Rajendran	33	m	apr 04	88	yes	yes	nil	nil	48	249	1	yes	nil	yes	yes	yes	gnb	nil	nil	g-ve	nil	nil	nil	nil	pm
Kartikeyan	33	m	jan 04	88	yes	yes	nil	nil	1	88	nil	nil	nil	nil	nil	nil	gpc	nil	nil	CONS	nil	nil	nil	nil	b
Shah nawaz	20	m	jul 06	203	yes	nil	nil	nil	1	246	nil	yes	nil	nil	nil	yes	nil	nil	nil	g-ve	nil	nil	nil	nil	b
Ramesh babu	26	m	apr 02	110	nil	yes	nil	nil	2	116	nil	yes	nil	nil	nil	yes	nil	nil	nil	nil	g-ve	yes	nil	mix	pm
Sasikumar	24	m	oct 05	88	yes	yes	nil	nil	9	334	1	yes	yes	yes	yes	yes	nil	nil	yes	nil	nil	nil	nil	nil	tb
Raghu	24	m	oct 02	96	yes	yes	nil	nil	24	90	nil	nil	nil	nil	nil	nil	nil	nil	nil	nil	nil	nil	nil	nil	tb
Ravi	31	m	aug 02	88	yes	yes	nil	nil	72	184	nil	nil	nil	nil	yes	yes	nil	nil	yes	nil	nil	nil	nil	nil	tb
Vijayalakshmi	31	f	oct 03	88	yes	yes	nil	nil	32	154	nil	nil	yes	yes	yes	yes	nil	nil	nil	nil	g+ cocci	nil	yes	mix	pm
Ravi	49	m	jan 06	86	yes	yes	nil	nil	1	88	nil	nil	yes	nil	nil	yes	nil	nil	nil	g-ve	nil	nil	nil	nil	b
Valli	22	f	jul 01	88	nil	yes	nil	nil	60	106	nil	nil	nil	nil	nil	yes	nil	nil	nil	g-ve	nil	nil	nil	nil	b
Ravichandran	37	m	july 02	88	yes	yes	nil	nil	13	123	nil	nil	nil	nil	nil	yes	nil	nil	nil	nil	nil	nil	nil	nil	uk
Kuttan	40	m	jul 00	96	yes	yes	nil	nil	4	105	nil	nil	nil	nil	nil	yes	nil	nil	nil	nil	nil	nil	nil	nil	uk
Yesuraj	17	m	apr 03	88	yes	yes	nil	nil	48	466	nil	nil	nil	nil	nil	nil	nil	nil	nil	nil	nil	nil	nil	nil	uk
Senthilkumar	20	m	nov 04	125	yes	yes	nil	nil	2	140	nil	nil	nil	nil	nil	nil	nil	nil	nil	nil	nil	nil	nil	nil	uk
Dakshinamurthi	46	m	nov 00	88	nil	nil	nil	nil			nil	yes		nil	nil	nil	nil	nil	nil	nil	nil	nil	nil	nil	uk
Chandran	42	m	mar 01	100	yes	yes	nil	nil	14	219	nil	nil	n	nil	nil	yes	nil	nil	nil	g-ve	nil	nil	nil	bacterial	b

Name	Age	Sex	Month of TX	cr at dis	Fever	Cough	Boe	Hemopt	LRTI mth	Creat Infect	No. of AR	ART	PTDM	HCV	CMV	Leucop	Spgs	Sp KOH	Sp AFB	Sp C/S	BAL g-s	BAL-koh	BAL -afb	BAL C/S	Org
Shankar	25	m	aug 01	88	yes	yes	nil	nil	46	184	nil	nil	nil	nil	nil	nil	gpc	nil	nil	nil	nil	nil	nil	nil	uk
Neethimaan	27	m	mar 04	90	yes	yes	nil	nil	7	155	nil	nil	nil	nil	nil	nil	nil	nil	nil	g-ve	g-ve	nil	nil	bacterial	b
Thangavel	38	m	feb 04	184	yes	yes	nil	nil	15	105	yes	yes	nil	nil	yes	yes	nil	nil	nil	nil	nil	nil	nil	nil	b
Ayeesha	21	f	jul 01	88	nil	nil	nil	nil			nil	yes		nil	nil	nil	nil	nil	nil	nil	nil	nil	nil	nil	uk
Panchalingam	35	m	jun 04	88	nil	nil	nil	nil	18	307	1	yes	nil	nil	nil	yes	nil	nil	nil	nil	nil	nil	nil	bacterial	b
Jeba kirubai	37	f	sep 03	88	yes	yes	nil	nil	3	123	1	yes	nil	nil	nil	yes	gnb	nil	nil	nil	nil	nil	nil	nil	uk
Valsa thangachan	33	f	apr 01	88	yes	yes	nil	nil	16	105	nil	nil	yes	nil	nil	yes	gpc	nil	nil	nil	nil	nil	nil	nil	uk
Selvakumar	22	m	sep 03	88	yes	yes	nil	nil	9	156	nil	yes	nil	nil	yes	yes	nil	nil	nil	nil	nil	nil	nil	nil	uk
Chidambaram	35	m	apr 02	105	yes	yes	nil	nil	13	150	nil	yes	nil	nil	nil	yes	nil	nil	nil	mix	nil	nil	nil	nil	pm
Manoharan	20	m	mar 05	88	yes	yes	nil	nil	15	105	nil	nil	nil	nil	yes	yes	nil	nil	nil	g-ve	nil	nil	nil	nil	uk
Ammani	43	f	aug 02	88	yes	yes	nil	nil	1	105	nil	nil	n	nil	nil	yes	nil	nil	nil	nil	nil	nil	nil	nil	b
Vishnu	19	m	apr 02	90	yes	yes	nil	nil	36	352	nil	yes	nil	nil	nil	yes	gpc, gnb	nil	nil	nil	nil	nil	nil	nil	uk
Manikandan	23	m	sep01	88	yes	yes	yes	nil	36	126	nil	nil	nil	nil	nil	yes	nil	nil	nil	nil	nil	nil	nil	nil	uk
Reena	23	f	sep01	88	yes	yes	yes	yes	60	144	nil	nil	nil	nil	nil	yes	nil	nil	nil	g-ve	nil	nil	yes	bact	pm
Lakshmi	26	f	apr06	88	yes	yes	yes	nil	1	88	nil	nil	nil	nil	nil	yes	nil	nil	nil	nil	nil	nil	nil	nil	b
Ramasamy	25	m	mar01	88	nil	nil	nil	nil			nil	nil		nil	nil	nil	nil	nil	nil	nil	nil	nil	nil	nil	pm
Irudayaraj	28	m	may02	88	yes	nil	yes	nil	1	88	nil	nil	nil	nil	nil	nil	nil	nil	nil	nil	nil	nil	nil	nil	pm
Anbu	22	m	feb 02	88	yes	yes	yes	yes	24	105	1	yes	nil	nil	nil	nil	nil	nil	nil	nil	nil	nil	nil	nil	uk
Senthil	32	m	mar03	88	yes	yes	yes	nil	2	105	nil	nil	nil	nil	nil	nil	nil	nil	nil	nil	nil	nil	nil	nil	tb
Moorthy	30	m	jan/01	88	nil	nil	nil	nil			nil	nil		nil	nil	nil	nil	nil	nil	nil	nil	nil	nil	nil	tb
Manoharan	50	m	jul/05	123	yes	nil	nil	nil	17	142	nil	nil	yes	nil	nil	nil	nil	nil	nil	nil	nil	nil	nil	nil	tb
Alibasha	27	m	may/05	88	yes	yes	nil	nil	13	123	nil	nil	yes	nil	yes	nil	nil	nil	nil	nil	gnb	nil	yes	bacterial	pm
Karthick	22	m	aug/03	123	yes	yes	yes	nil	27	228	1	yes	nil	nil	nil	yes	nil	nil	nil	nil	gnb	nil	nil	bacterial	pm
Munikumar	29	m	may/02	88	yes	yes	yes	nil	1	205	nil	yes		nil	nil	nil	nil	nil	nil	nil	nil	nil	nil	nil	pm

Name	Age	Sex	Month of TX	cr at dis	Fever	Cough	Boe	Hemopt	LRTI mth	Creat Infect	No. of AR	ART	PTDM	HCV	CMV	Leucop	Spgs	Sp KOH	Sp AFB	Sp C/S	BAL g-s	BAL-koh	BAL -afb	BAL C/S	Org
Geethalakshmi	43	f	aug 05	88	nil	nil	nil	nil			nil	nil		nil	nil	nil	nil	nil	nil	nil	nil	nil	nil	nil	tb
Kumari	36	f	jan 06	88	nil	nil	nil	nil	10	238	1	yes	yes	yes	yes	yes	nil	nil	nil	nil	nil	nil	nil	bacterial	b
Geethapalani	24	f	apr 03	88	nil	nil	nil	nil			nil	nil		yes	nil	nil	nil	nil	nil	nil	nil	nil	nil	mix	pm
Pmsekar	20	m	aug 01	88	yes	yes	yes	nil	2	123	nil	nil	yes	nil	nil	nil	nil	nil	nil	nil	nil	nil	nil	mix	pm
Punithalakshmi	25	f	aug 01	88	yes	yes	yes	nil	60	153	nil	nil		nil	nil	nil	gnb	nil	nil	nil	nil	nil	nil	mix	pm
Pushparani	29	f	aug 00	88	nil	nil	nil	nil			nil	nil		nil	nil	nil	nil	nil	nil	nil	nil	nil	nil	nil	b
Ravi	30	m	feb 01	88	nil	nil	nil	yes	48	221	1	yes	nil	yes	yes	yes	nil	nil	nil	nil	nil	nil	nil	nil	ATB
Senthilkumar	26	m	apr 04	88	yes	yes	yes	yes	30	96	1	yes		nil	nil	nil	nil	nil	nil	nil	yes	yes	yes	mix	pm
Sasikanthan	23	m	jan 01	96	yes	yes	yes	nil	12	195	1	yes	nil	yes	yes	yes	nil	nil	nil	nil	nil	nil	nil	nil	pm
Raja	30	m	mar 03	88	yes	yes	nil	nil	15		nil	nil		yes	nil	nil	nil	nil	nil	g-ve	gnb	nil	nil	pseudo omonas	b
Sakthivel	25	m	sep 02	88	nil	nil	nil	nil	15		nil	yes	yes	nil	nil	yes	nil	nil	nil	nil	nil	nil	yes	atb	ATB
Gomathinayagam	28	m	aug 03	88	nil	nil	nil	nil	4		nil	yes		nil	nil	nil	nil	nil	nil	nil	gnb	nil	yes	mix	pm
Musthafa kamal	38	m	may o2	88	nil	nil	nil	nil	15		nil	nil	yes	nil	nil	nil	nil	nil	yes	nil	nil	nil	nil	nil	tb
Reginamary	25	f	jun 03	88	nil	nil	nil	nil	38		nil	nil		nil	yes	yes	gnb	nil	nil	g-ve	nil	nil	nil	nil	b
Vinayagamurthy	32	m	apr 03	88	nil	nil	nil	nil	5		nil	yes		nil	nil	nil	nil	nil	nil	g-ve	nil	nil	nil	nil	b
Dandapani	33	m	apr 04	88	nil	nil	nil	nil	13		nil	nil		nil	nil	yes	nil	nil	nil	nil	nil	nil	nil	nil	fu